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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,732	03/24/2004	Young-Min Kim	Q109250	4429

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/807,732	KIM ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-14,16-20,22-24 and 54-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-14, 16-20, 22-24, 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 4, 15, 21, and 25-53 have been cancelled. Claims 54-57 have been newly introduced.

Applicant is advised that the present amendment to the claims is non-compliant as not all changes to the claims are shown. For example, claim 1 as submitted on 5/20/08 recited "a whole immunoglobulin." The word "whole" is not shown as being deleted from present claim 1. Applicant is advised that failure to properly mark all changes to the claims in the future will result in a Notice of Non-compliant Amendment. See 37 CFR 1.121.

Applicant's arguments filed 1/8/2009 have been fully considered but they are not persuasive.

Applicant has pointed out that in the request for continued examination (RCE) filed July 14, 2008, applicants expressly requested a suspension of prosecution for three months in order to have an opportunity for a further review of the issues. The Office Action dated October 8, 2008, was mailed before the expiration of the requested 3 months. As the requested 3 months have now passed and applicant has had an opportunity to further review the issues, the examiner will make this Office action non-final rather than vacating the prior Office action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5-14, 16-20, 22-24, and 54-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19, 27-37, and 39-45 of copending Application No. 10/535,232. Although the conflicting claims are not identical, they are not patentably distinct from each other because although worded differently, the conflicting claims embrace overlapping embodiments of protein conjugates.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3, 5-14, 16-20, 22-24, and 54-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/535,231. Although the conflicting claims are not identical, they are not patentably distinct from each other because although worded differently, the conflicting claims embrace overlapping embodiments of protein conjugates.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The co-pending claims recite a conjugate comprising an Fc fragment. As amended, the instant claims include Fc fragments as the immunoglobulin.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-14, 16-20, 22-24, and 54-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 has been amended to recite "covalently linked to one another in that order." Basis is stated to be in claims 2 and 18 and on pages 11-12. This is not agreed with. As is clear from the specification at page 12 and in claim 19, the immunoglobulin or physiologically active polypeptide can be linked to **either end** of the non-peptidic polymer. There is no required order. All that is required is that the non-peptidic polymer be between the immunoglobulin and physiologically active polypeptide. That is, B-X-A is an equivalent molecule to A-X-B. Note that the claimed conjugates are not directional in the way that a fusion protein is directional (with

an N- and C-terminus). There are two reactive groups at both ends of the non-peptidic polymer that do not require a particular orientation. The particular site of covalent bonding on the immunoglobulin and physiologically active polypeptide is not specified.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 7-8, 19-20, and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites "at least two complexes." There is no antecedent basis for "complexes" in claim 2.

Claim 7 is confusing in its dependency on claim 1. These claims recite all possible glycosylation states. As such, claim 7 doesn't clearly further limit the subject matter of claim 1.

Claim 22 indicates that the ratio of complex to immunoglobulin may be from 1:1 to 1:3. However, claim 18 requires that the ratio of the immunoglobulin to the non-peptidic polymer ranges from 1:5 to 1:10. It appears that claim 22 would need to be limited to physiologically active polypeptide to be consistent with claim 18. As claim 18 refers to the ratio of the immunoglobulin with the non-peptidic polymer and not a complex, this would imply that step (a1) of claim 19 is limited to coupling the non-peptidic polymer with the immunoglobulin for consistency. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-9, 11-14, 16-17, and 54-57 are rejected under 35 U.S.C. 102(e) as being anticipated by Heavner (US 2003/0211078).

Heavner discloses bifunctional molecules where PEG is bound at one end to a physiologically active polypeptide and at the other end to an immunoglobulin. The molecules have improved half life. The PEG has reactive groups at either end. Reactive groups specifically disclosed include maleimide and aldehyde. The PEG is linked to the amino terminal residue lysine or cysteine of the immunoglobulin or physiologically active polypeptide. The immunoglobulin can be an IgG, particularly IgG1. The proteins can be made recombinantly which would alter the nature of glycosylation depending upon the host cell in which it is produced. Physiologically active polypeptides include erythropoietin (EPO), cytokines such as tumor necrosis factor (TNF), blood proteins such as Factor VII. See abstract, figures, claims, Tables 1-4, Examples, paragraphs [0042, 0068-0075, 0086, 0091].

The molecules of Heavner et al. meet the structural and functional limitations of the claims. The claims do not require any particular amount or degree of increased half-life. The use of the term "comprising" permits the inclusion of additional components. The conjugate is not limited to only those components recited in the instant claims.

Applicant's arguments are unpersuasive. Heavner et al. does not require three or more identical target binding moieties. Heavner's invention is not limited to the claims of the reference. The instant claims do not exclude an antibody as being a ligand for a receptor as the physiologically active polypeptide. The instant claims recite "comprising" and do not exclude additional elements covalently attached to PEG (for example). See also instant claim 3 requiring multiple complexes. Applicant points to paragraph [0019]; however, this is a specific embodiment and at least paragraph [0018] and Table 1 provide a more general discussion of Heavner's conjugates. See also paragraph [0008] that discloses two different target binding moieties.

Claims 1-2, 7, 9-10, and 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Mohamed et al. (US 2006/0153839).

Mohamed et al. claims priority to and is entitled to benefit of 60/411,731. The effective filing date of Mohamed et al. is 9/16/02 and as such is valid prior art against the instant application.

Mohamed et al. discloses bifunctional molecules where PEG is bound at one end to a physiologically active polypeptide and at the other end to an immunoglobulin. Mohamed et al. discloses conjugating to PEG via succinimide derivatives. Example 6.2 conjugates a first antibody to PEG at a molar ratio of 1:3 (antibody:PEG)followed by separation via chromatography before further conjugating to the second antibody. The ratio of the complex to the second antibody is 1:2. See at least abstract, claims, and paragraphs [0112-0117] and [0226-0229]. An antibody that binds a receptor meets the definition of a ligand protein.

The molecules of Mohamed et al. meet the structural limitations of the claims. PEG would have been well known at the time of the invention to increase in vivo half life (as is clear from the prior art of record) and as such, the bifunctional molecules of Mohamed et al. would inherently possess this feature absent evidence to the contrary.

Applicant's arguments are unpersuasive. The antibodies discussed by Mohamed et al. would be in the IgG class. See at least paragraphs [0057-0058].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-22 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mohamed et al. (US 2006/0153839) in view of Rosen et al. (US 2004/0115165).

Mohamed et al. is applied as above but does not disclose the presence of a reducing agent such as cyanoborohydride. The ratios of immunoglobulin or physiologically active peptides to non-peptidic polymer recited in the claims are not specifically disclosed.

Rosen et al. claims priority to and is entitled to benefit of 60/428,809. The effective filing date of Rosen et al. is 11/25/02 and as such is valid prior art against the instant application.

Rosen et al. discloses using cyanoborohydride during PEGylation of bispecific molecules. See at least abstract and paragraph [0022].

It would have been obvious to use a reducing agent while conjugating PEG as in Mohamed et al. as a matter of routine experimentation. Rosen et al. makes clear that these reducing agents and techniques were routinely used in the art at the time of the invention to make bifunctional molecules with PEG. With respect to the range from 1:5 to 1:10 in claim 18, 1:2.5 to 1:5 in claim 20, and 1:1 to 1:3 in claim 22, Mohamed et al. discloses that using a ratio of 1:3 (protein:PEG) is sufficient for conjugation and that using a ratio of 1:2 (PEG complex:protein) is sufficient for the second conjugation. One of ordinary skill in the art would have been able to use more PEG in the conjugation reactions and any amount above this would have been expected to work and a matter of routine optimization.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is (571)272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa